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# Epilepsy: A Comprehensive Study

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# UNIVERSITY HONORS PROGRAM

## SENIOR PROJECT - APPROVAL

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PROJECT TITLE: Epilepsy: A Comprehensive Study

I have reviewed this completed senior honors thesis with this student and certify that it is a project commensurate with honors level undergraduate research in this field.

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## **Epilepsy: A Comprehensive Study**

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**ABSTRACT:** Epilepsy is the most common neurological disorder. The term epilepsy serves as an umbrella term to describe any faulty mechanism in the brain that causes an electrical storm, resulting in a seizure. These malfunctions may include problems with sodium channels, calcium channels, or with cell to cell interactions. Also, ensemble interactions play a role. Currently, there are various treatments which include medication, diet, surgery, and also an implantable device.

Other pertinent issues with epilepsy deal with social aspects. Sexual dysfunction is prevalent in epileptics. Epileptic women need to be aware of fertility problems. In addition, catamenial epilepsy affects many epileptic women. Pregnancy difficulties result both from the seizures themselves and from the teratogenicity of the medications. Sudden, unexplained death is also prevalent in epileptics. Also, memory problems are often associated with this condition. In addition, medication costs can plague epileptics.

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## **Mechanisms of Epileptic Seizures**

Epilepsy is the most common neurological disorder. It is presumed to affect from one half of one percent to one percent of the population. Epilepsy is a broad diagnosis for a number of neurological misfunctions that manifest themselves as different types of seizures. This chapter explores the possible causes of seizures.

Epileptic seizure can be characterized by two primary features, both of which are sufficient to produce seizure activity by themselves. The first is hyperexcitability of multiple neurons within a population. As will be shown, most of the means to produce this effect are normal basic mechanisms that have been deregulated. The second is hypersynchrony. Petit mal epilepsy is a common example of a clinical syndrome in which epileptiform activity involves primarily hypersynchronization. The abnormal discharge appears to result from a synchrony of widespread cell populations so great as to wipe out any functionally significant signals that might enter the central nervous system.<sup>1</sup>

An important component of the nervous system is its plasticity, the basic mechanism that supports change. However, this component can produce hyperexcitability and hypersynchrony that characterize epileptiform activities. Brain regions, such as the cortical structures, with best preparedness for plastic responses are most likely to be the focus of epileptiform activity. Three contributions to epilepsy's irregular neuronal function are intrinsic cell properties, cell-to-cell interactions, and ensemble interactions.<sup>2</sup>

There is great debate over whether there are "epileptic neurons" in populations of cells. These neurons were thought to be cells with "intrinsic abnormalities that drove the activity of normal neurons."<sup>3</sup> No cells with such qualities have been located by



researchers. However, scientists feel that there must be some abnormality at the single-cell level. Because many factors influence the cell's excitability, isolation in a research environment can show little evidence of being intrinsically epileptic.<sup>4</sup>

In the electronic structure of the molecule, recent studies have shown that synapses located closer to the initial segment have more powerful effects than synapses at more distant processes. This demonstration has caused much optimism in the field of neurology because the epileptic brain's cells may only have proximal dendrites. This structural change could contribute significantly to altering the transfer of synaptic current. In instances of abnormal increased activity, a small morphologic alteration has been found by researchers. This change could quite possibly explain the positive feedback that most epileptics experience.<sup>5</sup>

The depolarization of the membrane causes the opening of the sodium channel. This depolarization forms the upstroke of the action potential. These channels inactivate quickly and then no longer allow ionic flux. Thus when a neuron is significantly depolarized, spiking may quickly fade away. Repetition of discharge is critical to a cell's ability to participate in an aggregate of hyperexcitable neurons.<sup>6</sup>

In addition to this inactivating sodium current, a noninactivating sodium current has been found in many pyramidal neurons. Opening of this channel occurs with only small amounts of depolarization (from resting potential), and the current contributes in subtle, but important ways to the pattern of cell activity. For example, if the excitatory postsynaptic potential (EPSP)-induced depolarization is sufficient to open the noninactivating sodium channels, the depolarization booster mechanism is relatively

long-lasting because the current is noninactivating, and may be sufficient to bring subthreshold depolarizations to a suprathreshold level to initiate spike discharge.<sup>7</sup>

Calcium channels are divided into three categories. The first, the T-type channel, is considered low-threshold and is thought to help to synchronize cell populations. This channel can cause a burst of action potentials when it opens to admit calcium. This opening will further depolarize the cell. Some Petit mal seizures have been known to originate in deformities at these channels.<sup>8</sup>

Another type of calcium channel (L-type) remains closed at resting potential. It opens when the cell is depolarized by a great number of millivolts. The voltage-dependent calcium influx may add significantly to the depolarization. Summation can generate the burst discharges. The final channel is the N-type, whose role in the postsynaptic cell is unclear.<sup>9</sup>

Neurotransmitter is dependent on the voltage-dependent conductance in terminal membrane. N-type calcium channels contribute to the calcium influx while potassium repolarizes the cell membrane to prevent too much calcium from entering. The level and pattern of activity in single elements of a large interconnected population significantly affect the pattern of discharge in the population as a whole. Therefore, the epileptiform discharge is more likely when there is an increase in the level of excitability at the single-cell level, like in cases of spontaneous excitatory transmitter release.<sup>10</sup>

Cell-to-cell interaction can range from chemical transmission to ephaptic interaction. Modification of either of these activities can result in epileptogenesis. The loss of GABAergic inhibition is the foundation for a long held hypothesis in epileptiform activity. GABA is the primary inhibitory neurotransmitter in cortical structures. GABA-

a receptors mediate the inhibitory postsynaptic potentials (IPSPs). Binding of GABA to this receptor leads to the opening of chloride channels, causing hyperpolarization. However, because the voltage change depends on the resting potential, GABA might in fact cause depolarization. The GABA-b receptor is linked to a potassium channel through a guanosine triphosphate binding protein. The hyperpolarization accompanying this receptor is slow and long lasting. In the presence of moderate GABA-a blockade, the GABA-b mechanism successfully modulates duration of burst discharge. GABA release from interneuron terminals may be reduced by activation of GABA-b presynaptic receptors.<sup>11</sup>

Glutamate has long been recognized as the primary candidate for mediating fast excitatory synaptic transmission in the cortex and the hippocampus. Many glutamate-receptor subtypes exist. The primary ionotropic receptors (those associated directly with an ion pore) form two major subdivisions, NMDA-preferring receptors and non-NMDA receptors.<sup>12</sup>

On most occasions, excitatory postsynaptic potentials in cortical structures are produced mainly through activation of non-NMDA receptors. When this channel opens, it is permeated primarily with sodium and potassium ions. The NMDA receptor is more like GABA-a receptor in its complexity and various sites of modulation. This channel is voltage sensitive, being normally blocked by magnesium that binds to a site inside the channel. This magnesium blockade is relieved by cell depolarization, as may occur when excitatory synaptic input (mediated by non-NMDA receptors) depolarizes the membrane. Glutamate binds to the NMDA receptor then opens a channel that is permeable to both sodium and calcium. Calcium influx through NMDA channels triggers a number of



important processes. Long-term potentiation can be initiated by calcium influx through NMDA channels.<sup>13</sup>

The involvement of NMDA in epileptogenesis is suggested by findings of an enhanced NMDA component in the EPSP onto hippocampal neurons in kindled tissue and by significant NMDA contributions to EPSP's recorded in human epileptic cortical and hippocampal neurons. In addition to their voltage and magnesium control, NMDA receptors are modulated by glycine (necessary for function), zinc (inhibitory), and polyamines. As with the GABA-a receptor, NMDA receptors must be phosphorylated for efficient function. The potential importance of NMDA function is illustrated by the efficacy of NMDA channel antagonists in blocking late components of burst discharge in blocking late components of burst discharge in some models of epileptogenesis. The NMDA antagonist amino phosphonovalerate potently blocks initiation but is ineffective against already potentiated synaptic responses. This fact suggests that the NMDA mechanism is important in kindling of seizure development.<sup>14</sup>

Cell loss is common in the epileptic brain. Glutamate receptors are also important in mediating the cell damage so often associated with seizure discharge. Sclerosis is now seen as a potential trigger for significant circuitry organization that could further increase excitability. One proposed theory on cell loss is the calcium influx, mediated at least in part by NMDA receptors, leads to destructive processes in some cells. The NMDA antagonists can reduce or eliminate cell damage in ischemia or following high-frequency electrical stimulation. Damage is cell-type specific that can explain the high density of NMDA receptors on vulnerable neurons. Increases in intracellular calcium mediated by NMDA receptors may initiate complex intracellular mechanisms, through second and

third messenger systems, that are aspects of normal as well as pathological cell function. It has become clear that NMDA activation helps trigger complex changes in central nervous system neurons.<sup>15</sup>

Researchers are becoming more interested in other neurotransmitters as mechanisms and actions are being discovered. Acetylcholine has long been known to excite the central nervous system neurons. The muscarinic receptor action is mediated by a G-protein and generally involves slow changes in membrane potential (depolarizations) and increased input resistance, primarily through blockade of a potassium current. Similar effects occur with the application of noradrenergic beta-agonists. As a result of the action of such drugs, cell firing during membrane depolarization shows less adaptation, and hyperpolarizing afterpotentials are significantly reduced. Both effects contribute to increased excitability. However, the purpose of intrinsic cholinergic and noradrenergic systems in epileptogenesis is not fully known. Other neurotransmitters include somatostatin and cholecystokinin, neuropeptides with undetermined roles and mechanisms.<sup>16</sup>

Investigations have found that circuitry reorganization occurs as a result of seizures in humans. This change involves “sprouting” of axon branches and terminals that occur as a result of seizures in human and animal tissue. Sprouting has been seen as concurrent loss of cells. This evidence suggests that the sprouting axons “fill in” at synaptic sites where cell death has removed the normal presynaptic element. The granule cells themselves then expand their recurrent collateral field to occupy the vacated synaptic space.<sup>14</sup>

The excitability of the system could increase as a result of this reorganization process which could cause recurrent additional excitatory feedback. If inhibition is blocked, the sprouted dentate can be shown to be hyperexcitable. Electrical transmission does occur in the central nervous system. These interactions are mediated by gap junctions and are seen in both the hippocampus and the neocortex. This coupling provides a fast and secure means for synchronizing neuronal populations and could be important in the development of synchrony in epileptogenesis.<sup>17</sup>

Clearly not all hyperexcitability and hypersynchrony are the result of chemical transmission between cells. Ephaptic interactions, which are defined as synchronizations of cellular activity mediated by the flow of current through extracellular space, are suspected to be involved in normal cell functioning and in maintaining epileptiform activity in the absence of chemical transmission. Changes in extracellular space influence current flow and extracellular ion concentrations. Chronically epileptic tissue has shown that extracellular calcium concentration decreases during epileptiform bursting activity to levels that can not maintain strong synaptic connectivity in the recruitment and synchronization of cell discharge during seizures.<sup>18</sup>

The role of glial is considered important in epileptogenesis. Its function is thought to be the uptake of potassium from the extracellular space to protect the neuronal membranes and maintain appropriate levels of extracellular ion concentration. Glial infiltration into epileptic foci is common. This action is thought to be a response to high level of activity, because no deficits in glial function have been found to contribute to epilepsy. However, researchers have not ruled glial out because in some studies glia have shown active properties, such as spiking activity.<sup>19</sup>



Ensemble interaction is an important aspect of epilepsy because of the function of large populations of synchronously active neurons during epileptogenesis. If the seizure has a focus, then the way its activity is transmitted from focus to follower region is very important. Several mechanisms have been discussed concerning how terminals are excited. These include accumulation of extracellular potassium and release of excitatory transmitter, which proceeds to depolarize terminals. The spread of hyperexcitability is limited by the relationship of brain regions to activate those regions that they are synaptically coupled to. Another proposed mechanism is the accumulation of extracellular potassium ions. Potassium can be redistributed to other brain regions through diffusion or by means of glia in a relatively nonspecific manner. The extracellular ion buildup may be involved in recruiting neighboring brain areas into the hyperexcitability discharging region. Similarly, ephaptic interactions can recruit neurons in increasingly wider areas of tissue into synchronized discharge, especially when field potentials in the focal regions are large enough to reflect significant extracellular current flow.<sup>20</sup>

One of the most recent concepts to come out of epilepsy research is that of permissive gating, especially regarding the granule cells of the dentate gyrus. The dentate is a relatively inexcitable part of the hippocampal formation, often generating normal activity even in the face of highly abnormal discharge in CA1 and CA3 regions. Maximal activation of the dentate is now thought to be associated with seizure spread through hippocampus and into other brain regions. It is ideally situated to play a gating role because of the primary afferent input into the hippocampus is funneled through the granule cells. Researchers have speculated that the substantia nigra pars reticulata is



critical in the generalization of seizure activity. Data suggests that blocking the output of the nigra can curtail the development and spread of seizure activity. A similar gating role has been postulated for thalamic regions and for superior colliculus.<sup>21</sup>

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## **Treatments of Epilepsy**

Given the relatively complex concepts about how and where seizure activity is generated, the blockade of seizure activity can be accomplished in many ways, including antiepileptic drugs, surgery, the ketogenic diet, a new device, and a rectal gel.

One family of medications includes phenytoin, valporic acid, and carbamazepine. These drugs interfere with repetitive spiking activity by dampening pathogenic, activity of sodium channels. The adverse effects of phenytoin include anorexia, nausea, vomiting, aggression, ataxia, cognitive impairment, drowsiness, depression, headache, and paradoxical seizures.<sup>4</sup> Carbamazepine is used for partial and/ or secondary generalized seizures. Sodium valporate is used as a first line drug for partial and/or secondary generalized, generalized tonic clonic seizures without other seizure types, typical absence, myoclonic absence, atonic, tonic and most childhood absence seizure types. Carbamazepine has adverse effects including diplopia, dizziness, sedation, and induction of liver enzymes.<sup>4</sup>

Ethosuximide, trimethadione, and methosuximide appears to target low threshold calcium specifically, acting preferentially on cells whose activation pattern depends predominantly on these channels. Ethosuximide, another antiepileptic drug used specifically for petit mal epilepsy, acts on this channel to prevent a rise of a burst of action potentials that can develop when these channels open to admit calcium.(other book) The thalamic role in producing spontaneous rhythmic activity, dependent on low threshold calcium conductances, is believed to be specifically

antagonized by such drugs.

Tiagabine and vigabatrin enhance cerebrospinal levels of GABA by interfering with reuptake and degradation of GABA, respectively.<sup>1</sup> Tiagabine has been deemed effective in partial and secondarily generalized seizures. The adverse effects of Tiagabine include dizziness, asthenia, and tremor.<sup>2</sup> Vigabatrin is not limited to partial seizures. It has emerged as a potential first-choice AED against infantile spasms. The most common adverse effects of vigabatrin include drowsiness, dizziness, ataxia, tremor, amnesia, depression, weight gain, and hyperactivity in children. Recently visual field constriction, bilateral optic disc pallor, and subtle peripheral retinal atrophy have been linked to vigabatrin.<sup>2</sup>

Lamotrigine, like phenytoin and carbamazepine, blocks sodium channels.<sup>1</sup> This sodium channel blockade results in inhibition of glutamate release. There is increasing evidence that lamotrigine is effective against generalized seizures, particularly absence seizures.<sup>2</sup> Some of the most common dose-related adverse effects include dizziness, sedation, headache, diplopia, and ataxia.<sup>2</sup>

Another antiepileptic medication is Gabapentin. It is the first AED to be eliminated entirely by the kidneys.<sup>2</sup> Gabapentin is designed as a centrally acting GABA agonist, yet it apparently does not interact with GABA receptors nor does it interfere with GABA metabolism. It instead interacts with a novel binding site, which contains a specific protein found only on neurons in the central nervous system. This protein is found in highest density in areas of the



neocortex that are rich in synapses containing the excitatory neurotransmitter glutamine.<sup>1</sup> Adverse effects of gabapentin include somnolence, dizziness, ataxia, behavioral problems, weight gain, and movement disorders. Serious adverse events have been exceedingly rare.<sup>2</sup>

Topiramate has been identified as having at least three mechanisms of action. These include state-dependent blockade of sodium channels, potentiation of gamma-aminobutyric acid-mediated neuroinhibition, and blockade of glutamate-mediated neuroexcitation. This drug is effective in refractory partial seizures in adults, partial seizures in children, and generalized tonic-clonic seizures in children and adults. The most common adverse effects of topiramate include sedation, problem with concentration and word finding, decreased appetite, and weight loss. Nephrolithiasis has occurred in 1.5% of patients.<sup>2</sup>

Surgery is gaining increasing popularity as a method of treating patients who have focal seizures unresponsive to anti convulsant therapy. EEG recording with videotaping is important in localizing the site. Subdural electrodes are often used to determine the extent of the epileptogenic activity accurately. Other tests are used to assist in localization of seizure foci. These include neuropsychologic evaluations, the Wada test, SPECT, PET, and MRI studies. Temporal lobe resection is the most common surgery performed.<sup>2</sup> Although not always successful, surgery can relieve patients of the burden of medication and general dysfunction.

The ketogenic diet was frequently used for the treatment of intractable epilepsy before the discovery of the newer antiepileptic medications. The mode of action is unknown, but the seizure

control may be correlated directly with elevated levels of beta-hydroxybutyrate and acetoacetate that result from ketosis.<sup>3</sup> The ketogenic diet supposedly simulates the metabolism of a fasting body, which has been considered since biblical times an effective means to control seizures. This fast was then coupled with a high-fat diet in order to cause acidosis, ketosis, and increased levels of uric acid levels in the blood and urine without causing starvation.<sup>4</sup>

On July 16, 1997, the US Food and Drug Administration approved the first implantable device to reduce the number of seizures. It is seen as the pacemaker for the vagus nerve, whose stimulation produces an anti-epileptic effect by modulating the abnormal neuronal firing associated with seizures. When implanted, the device not only provides stimulation to the vagus nerve at regular intervals, but the patient also has a magnet that can stimulate the nerve at the onset of a seizure. The device is well tolerated and accepted by patients.

In July of 1997, Diastat was approved by the FDA. This drug is a gel formulation for rectal administration of the antiepileptic diazepam to stop clustered or prolonged seizures in progress. It is the first therapy prepared to be easily given in this manner ever to become available for in-home use in bringing potentially dangerous bouts of increased seizure activity under control. This drug will be able to give caregivers a greater sense of control. Trips to the emergency room are able to be greatly eliminated during bouts of unstoppable seizures. Somnolence and headaches were the two most frequently reported side effects in these studies.<sup>3</sup>

Epilepsy research is at a fast pace. Therefore, as more is learned about the functions, and

malfunctions, of the brain, more is done in developing medications designed to fit specific problems and patients. These newer medications are generally better tolerated by patients as they have fewer side effects. However, because of ethical obligations in test design, most new medications are only approved for add-on therapy. Neurologists, researchers, and patients all remain all remain hopefully that one day all epileptics will be able to say that they are seizure-free.

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## **Sexuality in Epilepsy**

Sexual behavior requires a normally functioning neuroanatomic substrate, which includes the frontal lobe and limbic structures, as well as adequate levels of hypothalamic, pituitary, and gonadal hormones. This behavior can be disturbed in epilepsy.<sup>1</sup>

Sexual behavior can be divided into two main components, desire and arousal. Desire reflects the individual's psychological health, cultural expectations, past sexual experiences, and requires salient sexual stimuli. Hormones are also required to support sexual desire. Those hormones include estrogen, progesterone, testosterone, lutenizing hormone, follicle stimulating hormone, and prolactin.<sup>2</sup>

Arousal is defined as the ability to respond to an appropriate stimuli with a series of stereotyped vascular, neural, and muscular responses. A normal sexual response requires an intact, functioning cerebral cortex, spinal cord, and autonomic nervous system. Genital structures must be normal. Hormones also play an important role.<sup>3</sup>

Sexual dysfunction was first described in people with epilepsy in 1956. Thirty to sixty percent of men with epilepsy have some disorder of desire or arousal, most often impotence. In a study conducted in 1985, 21 percent of men studied had never experienced sexual intercourse despite having the opportunity to do so. Also, in this same study at least one third of sexually active subjects had difficulty achieving and maintaining an erection or ejaculating.<sup>4</sup>

In epileptic women, there is a high incidence of dyspareunia, vaginismus, and arousal

insufficiency. One third of women described themselves as dissatisfied with their overall sexual function, compared with eight percent of the normal population.<sup>5</sup>

There are a number of potential mechanisms by which sexuality may be disturbed in people with epilepsy. Psychosocial deficits, such as restricted social opportunities and poor self-esteem, limit the opportunity for normal sexual interactions. Poor disease acceptance is associated with sexual dysfunction in other chronic illnesses, and may contribute to impaired sexuality in epilepsy. However physiological mechanisms may be more relevant than psychological variables. Disruption of cortical regions mediating sexual behavior, either by fixed lesions or by epileptiform discharges, could influence sexual desire and arousal. Changes in hormones supporting sexual behavior occur in epilepsy, both because of seizures and antiepileptic drugs. Antiepileptic drugs have direct effects on conical regions mediating sexuality and may also cause sexual dysfunction by secondary effects on reproductive hormones.<sup>6</sup>

Psychosocial disability can adversely impact sexuality in men and women with epilepsy. Individuals with epilepsy are susceptible to poor self-esteem. Recurrent seizures may lead to a sense of vulnerability and helplessness, impairing the capacity to form healthy, nurturing relationships. Having epilepsy may limit social development, particularly for patients with frequent seizures who have restricted access to usual educational and occupational experiences. Individuals also express concern that sexual activity will precipitate a seizure, particularly those whose seizures are sometimes triggered by hyperventilation or physical exertion.<sup>7</sup>

Several clinical observations suggest that dysfunction in limbic structures predisposes to sexual dysfunction. Sexual dysfunction usually arises after the onset of seizures. It is most common in individuals with localization-related epilepsy, particularly those whose seizures arise from the amygdala and hippocampus. Reports show that sexual dysfunction improves after temporal lobectomy for medically intractable seizures.<sup>8</sup>

Alterations in pituitary and gonadal hormones can negatively impact sexual behavior in people with epilepsy. In both epileptic men and women, interictal levels of prolactin are elevated because of seizures. Elevated prolactin is one of the most frequent causes of impotence in otherwise healthy males. The free fraction of sex steroid hormones may be reduced in individuals with epilepsy. Low levels of free testosterone have been associated with disorders of sexual desire and arousal in men.<sup>9</sup>

Sexual dysfunction may also be a consequence of ictal alterations in neurotransmitters, including gamma amino-butyric acid (GABA), opioids and serotonin. In a study using rabbits, elevations in GABA inhibit sexual behavior. Serotonin agonists specific to one receptor subtype inhibit sexual desire and sexual arousal in rats.<sup>10</sup>

Antiepileptic drugs affect sexual behavior by at least two mechanisms—alterations in hormone metabolism and binding, and by direct cortical effects. They may induce or inhibit the hepatic microsomal enzyme system and alter metabolism of sex steroid hormones. Many antiepileptic drugs also induce production of sex hormone binding globulin (SHBG), a binding



protein for steroid hormones. Increased binding reduces the free, biologically active fraction. These two mechanisms cause a reduction in the free level of steroid hormones. Antiepileptic drugs are also associated with elevations in prolactin and gonadotropins. Antiepileptic drugs may act as suppressants of sexual behavior. Diminished libido and arousal were described in 12% of men beginning an antiepileptic drug.<sup>11</sup>

AED's do not cause all sexual deficits observed in people with epilepsy. First, sexual dysfunction generally arose with the onset of epilepsy- prior to treatment. Sexual deficits may improve when seizures are controlled, even if a higher dose of antiepileptic drug is required or a temporal lobectomy is performed.<sup>12</sup>

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## **Fertility Problems in Epilepsy**

Women with epilepsy have fewer children than women in the general population. Their fertility rate is 25 to 33 percent lower than the average. Social pressures on women with epilepsy to refrain from having children may be a factor in their lower rate of childbearing. However, studies reveal that biological factors rather than social factors play a role in the higher rates of infertility in women with epilepsy.<sup>1</sup>

Menstrual irregularities are seen more often in women with epilepsy than in women who do not have the disorder. Research has demonstrated a high proportion of reproductive and endocrine disorders in women with epilepsy, which can affect their ability to conceive or carry a child to term.<sup>2</sup>

Menstrual abnormalities and gynecologic syndromes such as polycystic ovaries, hypogonadotropic and hypergonadotropic hypogonadism, oligomenorrhea, and amenorrhea are more common in women with epilepsy. A probable cause for this is the effect of antiepileptic medication on the hypothalamic-pituitary axis, or indirectly through alterations in the metabolism of sex steroids. Women with temporal lobe epilepsy are particularly prone to anovulation. Dysfunction of the limbic cortex, which is extensively interconnected with the hypothalamus, appears to alter the release of hypothalamic hormones and pituitary gonadotropins, resulting in anovulation.<sup>3</sup>

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## **Catamenial Epilepsy**

Catamenial epilepsy is defined as a cyclic increase in epileptic attacks which coincide with menses. In early times, these changes were attributed to the moon. In 1885, Gowers first examined the association of menses and epilepsy.<sup>1</sup>

Catamenial epilepsy is observed in 10 to 70% of women with epilepsy. This wide range in incidence is due to the lack of a more specific definition of catamenial epilepsy. 70% of women claim that their seizures are exacerbated by menstruation. However, the strict definition states that catamenial epilepsy is epilepsy that occurs at or worsens around menstruation, and can be demonstrated in 12% of women with epilepsy. These menstrual exacerbations occur with all types of seizures.<sup>2</sup>

Several investigators show that even nonepileptic women exhibit minor EEG fluctuations during the menstrual cycle. In 1942, Dusser de Barenne and Gibbs discovered cyclical background slowing during two menstrual phases: the time of menstrual flow and the time of ovulation. Other studies reveal a drop in the amplitude of the EEG during the premenstrual and menstrual phases.<sup>3</sup>

Catamenial epilepsy is believed to result from cyclic alterations in both ovarian hormone levels and drug metabolism. In women with catamenial epilepsy, seizures frequently start at or shortly after menarche. Many of these women show increased electroencephalographic activity during menstruation. Seizure threshold is increased by progesterone and decreased by estrogen,



an effect presumably caused by alterations in brain excitability. Frequency of seizure activity has been shown to increase during two specific times in the menstrual cycle. The first corresponds to the rapid decrease in progesterone just before menses and the second to the elevation of estrogen before ovulation. An increase in frequency is also seen during anovulatory cycles when progesterone levels are relatively low. Menopause or oophorectomy may lead to significant improvement in epilepsy.<sup>4</sup>

Pregnanolone, a main metabolite of progesterone, modulates the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), and augments the GABA-induced chloride current in hippocampal neurons. It is hypothesized that endogenous neurosteroids including pregnanolone, may decrease when progesterone concentrations fall before menstruation, reducing the inhibitory effects of GABA and causing seizure exacerbation.<sup>5</sup>

A 1986 study by Rosciszewska, Bunter, Guz, and Zawisza showed that seizure incidence during the menstrual cycle is connected with a deficit of progesterone rather than elevated oestrogen levels. In the study, the lowest number of seizures was noted when progesterone reached its highest level. The "protective effect" of progesterone on brain activity in women can be confirmed by the use of synthetic progesterone in the therapy for catamenial epilepsy. A related study showed a reduction of seizure frequency in 7 of 10 women treated with medroxyprogesterone.<sup>6</sup>

Females with so-called catamenial epilepsy had premenstrual tension more frequently. This

difference is connected with greater endocrine disturbances and changes in water-electrolyte balance. Thus, the effect of this syndrome on serum concentration of anticonvulsants during premenstrual phase can not be neglected.<sup>7</sup>

A new controversy has erupted on the radical remedy of bilateral oophorectomy in order to treat catamenial epilepsy. It is seen as a last result in patients with epilepsy that can not be controlled by any of the appropriate and accepted treatments. A case in Liverpool studied a woman who had tried hormonal treatment, regular antiepileptic drug treatment, and combination antiepileptic drug treatment. When she became pregnant, she experienced no seizures until after delivery. Finally a total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. She has had no seizures since the surgery.<sup>8</sup> Other doctors argue that this treatment was too radical. They believe that epilepsy should be fully identified by the specific syndrome and have the accepted treatment possibilities exhausted before these unsubstantiated remedies are used.<sup>9</sup>

Menstrual abnormalities and gynecologic syndromes such as polycystic ovaries, hypogonadotropic and hypergonadotropic hypogonadism, oligomenorrhea, and amenorrhea are more common in women with epilepsy. A probable cause for this is the effect of antiepileptic medication on the hypothalamic-pituitary axis, or indirectly through alterations in the metabolism of sex steroids. Women with temporal lobe epilepsy are particularly prone to anovulation. Dysfunction of the limbic cortex, which is extensively interconnected with the hypothalamus,

appears to alter the release of hypothalamic hormones and pituitary gonadotropins, resulting in anovulation.<sup>10</sup>

Medication levels are known to fluctuate at different times throughout the cycle. Decreased serum levels of phenytoin demonstrated during menses in women with catamenial epilepsy correlate with increased seizure activity. "The decrease in estrogen and progesterone at menstruation is believed to stimulate the release of hepatic monooxygenase enzymes which accelerates the risk" of seizures. Recommended treatment of catamenial epilepsy includes measurement of serum levels of anticonvulsants during times of seizure exacerbation. Sometimes an altered dosing schedule is recommended for seizure control.<sup>11</sup>

Some investigations have shown that progesterone therapy is beneficial. In addition to antiepileptic properties, progesterone may work by suppressing gonadotropin release which, in turn, lowers estrogen levels. The effects of combined oral contraceptives on frequency of seizure have been inconsistent, with seizure exacerbation occurring on pill free days. Uninterrupted combined use of oral contraceptives or the progestin-only oral contraceptive may be preferable in women with epilepsy as they result in continuous progestin exposure. Because of the decrease of efficacy of oral contraceptives in patients with epilepsy receiving anti-convulsant therapy due to altered metabolism of the contraceptive steroids, a higher dose of oral contraceptive pills are recommended.<sup>12</sup>

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## **Epilepsy and Pregnancy**

Pregnancy in epileptic women is a growing concern in society. Women with epilepsy who become pregnant are frequently considered to have a high risk of an adverse outcome.<sup>1</sup> Congenital abnormalities are increased two to three times over the normal population.<sup>2</sup> Not only are the seizures themselves harmful to the child, but also the anti-epileptic drugs, AED's, prove a threat to the child. Nekane et al., 1980, studied the incidence of newborn malformations born to epileptic women. The study revealed that congenital malformations were least in newborns of women not taking medication, but remaining seizure free. The highest prevalence was among women who both had seizures and took AED's. Women having seizures but not taking medicine and women without seizures but taking medication occupied an intermediate position. In addition to the seizures and the medication, the changing metabolism of the mother can prove challenging to the doctor.<sup>3</sup>

Many women experience changes in drug metabolism during pregnancy. 25-30% of women experience an increase in seizure frequency and severity during pregnancy.<sup>4</sup> Because there is an increase in circulating serum proteins, a decrease occurs in the blood level of free, active drug. Therefore, physicians recommend that the free rather than total, serum drug level should be monitored in pregnant patients. The normal increase in extracellular fluid may also cause fluctuations in antiepileptic drug levels. Other factors that may suppress drug levels are delayed gastric emptying and hyperemesis. Physicians also cite noncompliance with medications, hyperventilation, dilutional hypocalcemia and hyponatremia, emotional stress and sleep

deprivation as factors contributing to seizure frequency and intensity increases.<sup>5</sup>

The seizure itself can be harmful during pregnancy. A tonic-clonic seizure can result in blunt abdominal trauma often causing premature rupture of membranes.<sup>6</sup> These seizures have also caused fetal intra-cranial hemorrhage, miscarriage, fetal neonatal, and prenatal death.<sup>7</sup> Also, fetal heart rate decreases during a seizure. If the mother has a seizure in the first trimester there is an increased rate of spontaneous miscarriage and an increased risk in fetal malformations. These effects are likely due to transient fetal hypoxia and acidosis secondary to altered uteroplacental circulation.<sup>8</sup>

A decrease in fetal viability is seen in children of epileptic mothers. These infants are also more likely to have lower Apgar scores. A decrease in fetal growth is also apparent in infants of epileptics. These children are more likely to be small for gestational age. Seven to ten percent meet the criteria for low birth weight. Also four to eleven percent are born premature.<sup>9</sup>

An increased risk of fetal bleeding is seen in children exposed to AED's in utero. Phenytoin, primidone, and phenobarbital are known to inhibit transport of vitamin K across the placenta. Therefore, there is a decrease in fetal vitamin K-dependent clotting factors (II, VII, IX, X). Fetal hemorrhage within 24 hours after birth is a probable outcome. Treatment for these infants includes additional vitamin K, and fresh frozen plasma to correct the coagulopathy.<sup>10</sup>

Scientists have targeted AED's as having teratogenic effects. All AED's have been found to be teratogenic.<sup>11</sup> The greatest risk of congenital malformation comes with exposure to AED's

during the third to eighth week after conception.<sup>12</sup> Minor digital and midfacial abnormalities are seen in 5-30% of infants of women with epilepsy.<sup>13</sup> Other malformations include neural tube defects and heart defects.<sup>14</sup> Polytherapy and higher drug levels are associated with an increased risk of malformations.<sup>15</sup> Cardiac defects are linked to phenobarbital, phenytoin, and primidone. Trimethadione is not recommended for a pregnant mother because it produces severe birth defects, mental retardation, and developmental delay in about 50% of offspring.<sup>16</sup>

Of all the AED's, the hydantoins are most commonly associated with adverse pregnancy outcomes. Approximately 1 in 500 pregnancies have had fetal exposure to phenytoin, the most common hydantoin. Fetal hydantoin syndrome occurs in 10-30% of exposed pregnancies. Common symptoms of the syndrome include growth deficiency, central nervous system dysfunction (e.g., mental retardation), craniofacial anomalies, increased risk of major malformations and nail/digit hypoplasia. School and learning problems, developmental problems, and physical abnormalities, such as nail hypoplasia and growth failure, are significantly higher in those affected by the syndrome. Increased risk for recurrence in subsequent pregnancies is shown by studying families with two exposed children. In this study, either both or neither were affected. Children exposed to phenytoin had an average global intelligence quotient (IQ) 10 points lower than controls.<sup>17</sup>

Carbamazepine is another AED shown to have teratogenicity. In one study 50 women took carbamazepine as monotherapy. 35 gave birth to exposed infants with the following



abnormalities: craniofacial defects (11%), fingernail hypoplasia (26%), and developmental delay (20%). The syndrome causing these results was named "fetal carbamazepine syndrome". Children with this syndrome also exhibit slow development and low IQ scores. In a dosage study, carbamazepine given at the highest dosage caused a significant decrease in fetal body weight, a 2.9-fold increase in fetal resorptions, and a 29% decrease in maternal weight compared to controls. Soft tissue and skeletal malformations increase sixfold.<sup>18</sup>

Valporic Acid, VPA, also has teratogenic effects. It has been linked to spina bifida with a 1-2% risk with maternal use. Fetal valproate syndrome has been described. Symptoms include craniofacial anomalies, with minor abnormalities in ear shape or position being common, congenital heart defects. Developmental delay occurs in more than two-thirds of the cases exposed to monotherapy. Recently it has been reported that neurologic performance is still impaired at 6 years of age.<sup>19</sup>

Fetal benzodiazepine syndrome is frequent in children born to mothers taking benzodiazepines. Frequent symptoms include short nose with a low nasal bridge, and upturned nose and epicanthic folds. Other symptoms include slanting eyes, low-set or abnormal ears, and a hypoplastic mandible. Children also had delayed neurodevelopment. Infants exposed to both VPA and benzodiazepines had more pronounced abnormalities than those receiving monotherapy. In one study, 64 out of 80 infants receiving benzodiazepines in utero had sedation and withdrawal symptoms at birth. Fifty had no developmental anomalies, but 6 had conditions consistent with



teratogenicity.<sup>20</sup>

Primodine and phenobarbital are associated with fetal anomalies similar to those associated with other AED's. Symptoms include both pre- and postnatal growth failure, hirsutism, microcephaly, mental retardation, hypoplastic nails, and craniofacial anomalies such as short nose, ptosis of the eyelids, low-set ears, and CP. Prenatal exposure to phenobarbital exposure has been shown to lower verbal intelligence score in adult men tested in a recent study.<sup>21</sup>

Trimethadione is contraindicated in pregnancy. It produces severe birth defects, mental retardation, and developmental delay in fifty percent of offspring. Therefore, a woman of childbearing age should not take trimethadionine.<sup>22</sup>

The teratogenicity of the newer antiepileptic drugs are not well documented. However, some information is obtained by the preclinical studies. Felbamate did not show birth defects in rats or rabbits. Gabapentin at high doses was toxic to rodent fetuses. Delayed ossification of bones was also noticed. Lamotrigine is a weak inhibitor of dihydrofolate reductase, and antifolate activity is associated with teratogenicity. Topiramate showed growth retardation and limb agenesis. Tigabine has shown growth retardation in animal studies.<sup>23</sup>

The risk of the child of an epileptic having epilepsy is increased to two to four percent compared with one percent for the general population. Also a significant risk of fetal death is present, although this risk has been minimized with the growth of knowledge on the subject. Sedation may occur in the infant if it ingests phenobarbital from breast feeding. Most mothers

taking AED's can breast feed.<sup>24</sup> However, phenobarbital or primidone should be used with caution by nursing women. Women taking gabapentin, topiramate, or tiagabine should nurse only when the benefits outweigh the risks. Mothers taking lamotrigine are not recommended to breast feed. The manufacturer of felbamate suggests it be used with caution in nursing women.<sup>25</sup>

Multiple antiepileptic drugs have been shown to increase risk profiles. "When carbamazepine, phenobarbital, and VPS are combined with or without phenytoin, 58% of infants have birth defects."<sup>26</sup> This is higher than with other three- to four-drug combinations, suggesting metabolic interactions. VPA inhibits epoxide hydroxylase, which increases the presence of epoxide metabolites of aromatic AED's.

Maternal folate concentrations normally decline during pregnancy. AED use may cause further decreases, thereby increasing the risk of folate deficiency. In one study, phenytoin and phenobarbital produced the greatest decrease in serum folate. Serum folate and RBC folate concentrations were significantly lower in women having spontaneous abortions or children with major malformations compared with those with normal outcomes. Pregnant women taking multiple anticonvulsants tended to have an increased risk for folate deficiency compared with those receiving monotherapy. Women were more likely to have an adverse pregnancy outcome when serum folate was less than 4 microgram/ mL before pregnancy.<sup>27</sup> Phenytoin, carbamazepine, phenobarbital, lamotrigine, and possibly valproate have been found to have antifolate activity.<sup>28</sup> Findings in multiple studies showed that all women taking AED's should also receive

supplemental folic acid.<sup>29</sup>

Oral contraceptives reduce both serum folate and RBC folate levels. Serum folate concentrations decrease with chronic use of oral contraceptives and normalize within 3 months after discontinuing the oral contraceptive. Epileptic women taking oral contraceptives and AED's may be at higher risk, since they are taking more than one folate-lowering drug, and may experience contraceptive failure caused by enzyme-inducing AEDs. More studies are needed in order to see the true effects.<sup>30</sup>

Reactive epoxide metabolites may be responsible for AED-induced teratogenicity. Phenytoin, carbamazepine, phenobarbital, felbamate, and lamotrigine may be metabolized to form epoxides. Adding valproic acid to any of these AED's may increase the risk, because this drug inhibits epoxide hydrolase, thereby increasing epoxide concentrations. Folate deficiency could further increase epoxide concentrations of aromatic AED's.<sup>31</sup> AED's may be particularly dangerous in women predisposed to give birth to infants with neural tube defects. These women may not utilize folate as efficiently as other women and AED use diminishes serum folate concentrations.<sup>32</sup>

Physician recommendations for epileptic mothers include the following:

1. Use a first-choice antiepileptic drug for seizure type and epilepsy syndrome.
2. Use the AED as monotherapy and at the lowest dose possible that protects against tonic-clonic seizures.



3. Monitor plasma AED levels monthly and, if possible, obtain free or unbound levels.
4. Avoid polytherapy, especially combinations of valproate, phenobarbital and carbamazepine.
5. Avoid valporate and carbamazepine when there is a family history of neural tube defects.
6. Begin folate supplementation in the preconception period.
7. When using valporate, avoid high plasma levels and divide the dose over three to four administrations per day.<sup>33</sup>

In addition to the above, physicians often recommend women delaying pregnancy until seizures are adequately controlled. Also, amniocentesis and level II ultrasound at 16-18 weeks should be performed to check for neural tube and cardiac malformations. Vitamin K should be given to mother from her 36th week on and also given to the baby at birth.<sup>34</sup> Some physicians also recommend a gradual discontinuation of antiepileptic drugs if a woman is seizure-free with a normal encephalogram for at least two years.<sup>35</sup>

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## **Sudden Death and Epilepsy**

Sudden unexpected, unexplained death (SUD) is more common in patients with epilepsy compared with the general population. The mechanism is unclear, but there are several theories. These include cardiac tachy- or bradyarrhythmias related to paroxysmal autonomic dysfunction, respiratory arrest and neurogenic pulmonary oedema, and events occurring in connection with overt or subclinical seizures. Low or undetectable post-mortem blood concentrations of antiepileptic drugs has been a frequent finding in cases of SUD. Although these reports have been questioned based on their methodology, they have raised questions regarding sudden drug withdrawal or non-compliance as precipitating factors for SUD.<sup>1</sup>

The antiepileptic drugs carbamazepine and phenytoin are sodium-channel blockers with a membrane stabilizing effect in the central nervous system as well as in the cardiac conduction system and myocardium. Carbamazepine may induce cardiac bradyarrhythmias, which has caused safety concerns, and phenytoin has been used and classified as an antiarrhythmic drug. A sudden withdrawal of such cardioactive drugs might theoretically induce both direct and indirect cardiac changes of relevance for SUD unrelated to seizure activity.<sup>2</sup>

A recent study demonstrated that abrupt withdrawal of antiepileptic treatment reduced heart-rate variability suggesting an altered autonomic modulation, which in other patient populations has been associated with increased mortality. The withdrawal of these drugs induced an expected reduction in bradycardias in a subgroup of patients. However, there was also an



unexpected 10-fold increase in ventricular premature beats in some patients suggesting increased electrical instability. Since reduced heart-rate variability signals a state of increased electrical vulnerability and ventricular premature beats might trigger life-threatening ventricular arrhythmias the findings of the experiment point to two important factors that might contribute to an increased risk for sudden death during abrupt withdrawal of sodium-channel-blocking antiepileptic drugs even in the absence of seizures.<sup>3</sup>

### References

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## **Memory and Epilepsy**

Cognitive dysfunction has long been known to accompany seizure activity. There are many different factors affecting memory. These include the underlying cause of the epilepsy, seizure type, frequency and severity of seizures, undetected seizures, psychosocial factors such as mood and expectations and antiepileptic drugs.<sup>1</sup> It is agreed that memory function improves as the control of seizure improves.<sup>2</sup>

Structural cerebral abnormalities which underlie the epileptic focus often directly cause cognitive dysfunction. However, epileptic foci arising distant from those brain structures known to be involved in learning and memory may also be associated with disorders of learning and memory. Excision of epileptic foci was shown to improve cognitive function in experimental models in primates.<sup>3</sup>

It appears that seizure activity incrementally causes an indiscriminate and widespread induction of long-term potentiation, consuming and thereby reducing overall hippocampal plasticity available for information processing. Because the seizure activity appears to consume the synaptic plasticity available in otherwise healthy brain tissue making the formation of new memories is disrupted, and may represent a mechanism by which cognitive function is impaired in epileptic humans.<sup>4</sup>

The physiological and cognitive effects can be modulated by NMDA receptor-associated channel blockade. This suggests that future therapeutic strategies directed towards the

preservation of hippocampal synaptic plasticity may prove effective in the attenuation of epilepsy-associated cognitive impairment. Unfortunately, presently available drugs active at the NMDA receptor site (such as ketamine) can only be used effectively where seizure activity can be precisely predicted, as in electroconvulsive therapy.<sup>5</sup>

## References

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